

S/N 10/081,050



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	David W. Osborne	Examiner:	Lakshmi S.Channavajjala
Serial No.:	10/081,050	Group Art Unit:	Unknown
Filed:	February 20, 2002	Docket No.:	1195.346US1
Title:	Topical Dapsone for the Treatment of Acne		

Declaration Under 37 C.F.R. §1.132 of Robert Lathrop

I, Robert W. Lathrop, declare and state that:

1. I am a trained dermatology scientist. From 2000 to the present, I have held the position of Scientist in the topical applications division of Atrix Laboratories Inc., Fort Collins, Colorado. From 1990 to 2000, I was a Formulations Scientist in the dermatological division of Dow Pharmaceutical Sciences, Petaluma, California. I hold a BS degree in Biological Sciences from Colorado State University, Fort Collins Colorado, 1976 and have successfully completed an extensive graduate study program in botany sciences at Colorado State University, 1978-1983. I have been a topical and dermatological formulations scientist working in the field of skin, mucous membrane and topical surfaces technology for approximately 15 years.
2. I am familiar with the technology described in U.S. Patent Application Serial No. 10/081,050. That technology concerns a new method of treatment using a known composition. In particular, that technology is based upon the discovery that an anti-microbial, topical Dapsone composition known for use in treatment of inflammatory infections such as that occurring with inflammatory acne is also useful for treatment of non-inflammatory acne.
3. I understand that in the course of examination of this patent application in the U.S. Patent Office, the examiner has rejected the claimed method of treatment over U.S.

Patent No's. 6,060,085 and 5,863,560 (the Osborne references). These Osborne references name Dr. David Osborne as inventor. He is the same David Osborne named as inventor on the present application. The Osborne references indicate that Dapsone is an anti-microbial agent having anti-inflammatory properties (col. 3, lines 9-11; col. 4, line 66-col. 5, line 1, USP 5863560). The Osborne patents focus upon the anti-inflammatory and anti-microbial properties of Dapsone for treatment of acne (col. 7, line 65-col. 8, line 9, USP 5863560).

4. While the Osborne references do not recite the use of a Dapsone composition for treatment of non-inflammatory acne, I understand that the examiner believes it is inherent that such Dapsone composition would treat non-inflammatory acne when it is used to treat inflammatory acne. This belief is erroneous, however. I will explain the errors and the appropriate view of acne as a result of my experience as a dermatological formulations scientist.

5. While, at first glance, non-inflammatory acne and inflammatory acne and the treatment of these conditions may seem to be the same, in practice, these kinds of acne and these treatments substantially differ. I have attached several internet articles describing these differences. They are:

a) *American Family Physician*, October 15, 2000,
www.aafp.org/afp/20001015/1823.html,
dated November 11, 2004;

b) *Health Newsflash*, "Acne Causes, Symptoms and Acne Treatment"
www.healthnewsflash.com/conditions/acne.htm,
dated November 11, 2004;

c) *Acne in Adolescents*, www.home.coqui.net/myrna/acne.htm,
dated November 11, 2004.

6. As shown by these internet articles, there are at least two kinds of acne. They differ substantially and the first kind of acne, non-inflammatory acne, does not invariably become the second kind of acne, inflammatory acne. Non-inflammatory acne does not involve infection by *P. acnes*. See *American Family Physician*, page 2. The first kind of acne is familiar to most persons as “black-heads”, also known as comedones. As most persons are well-aware, “black-heads” often do not swell or form pustules or become inflamed with reddened surrounding skin. Instead, “black-heads” such as those often appearing on the nose, are plugs or comedones of keratinaceous material formed of dead skin cells, sebum and lipids. The comedones fill the follicular canals or skin pores adjacent the hair follicles. Often, the comedones appear as black spots on the skin as a result of oxidation of the melanin present in the comedone. The “black-heads” do not involve reddened skin, do not involve skin eruptions and do not contain pus or serous fluid. “Black-heads” most often do not become infected. “Black-heads” are sometimes the acne plaguing teenagers; however, more often they are the acne plaguing mature adults.

7. In contrast, the second kind of acne constitutes a significant dermal infection of *P. acnes*. Inflammatory acne is signified by reddened surrounding skin, skin eruptions, swelling around the infected pore, as well as pus and serous fluid within the infected pore and within the dermis tissue surrounding the pore. There is an invasion of mast cells, immune cells and antibodies at the local dermis site as well as a histamine response causing the skin to redden, swell and erupt. The invasion of immune cells and the like combats the growing colony of microbes (*P. acnes*). This invasion results in the formation of pus and serous fluid within the dermis surrounding the pore and within the pore itself. Many persons are familiar with this kind of acne as it is painful, unsightly and can lead to significant skin damage such as pock marks and acne scars. Inflammatory acne especially plagues teenagers but is not a significant problem among mature adults.

8. Treatment of these two kinds of acne differs significantly. For “black-heads”, the treatment involves use of keratolytic agents, astringents, dissolving agents and surfactants

such as soap and water or alcohol. These agents and techniques soften, loosen and otherwise remove the comedones from the respective pores. However, since there is no infection, anti-microbial agents are not used. In fact, the use of significant anti-microbial agents such as penicillin or tetracycline would require a prescription from a registered physician. Such agents are NOT prescribed for treatment of “black-heads”. Note that the Table, page 4, *American Family Physician* indicates that topical antibiotics may be helpful if inflammatory lesions are present. Physicians understand that because there is no microbial infection, anti-microbials are counter-indicated. Physicians do not prescribe anti-microbials unless there is a demonstrated presence of a microbial infection.

9. For treatment of inflammatory acne, physicians prescribe systemic and topical antimicrobial agents. Agents such as penicillin, tetracycline, cephalosporin, erythromycin and Dapsone are some of the anti-microbials useful under prescription for such treatment. The goal is to kill the *P. acnes* colony that has begun to grow in the dermis. In such an infection, the microbial colony grows not only in the closed pores but also within the dermis surrounding the pores. In short, inflammatory acne is a true bacterial infection of the skin. Use of these anti-microbial agents is not indiscriminate. Because they are available only by prescription, a physician would provide them only for treatment of inflammatory acne. If one only had “black-heads”, one would not have such a prescription medicine on hand. Note that the attached article, *Acne Causes, Symptoms and Treatment*, indicates on page 16 that topical antibiotics are prescribed for moderate to severe inflammatory acne but not for “blackheads.”

10. One of skill would also understand that Dapsone formulations would only be available by prescription, not over the counter. Dapsone is an anti-leprosy drug that requires frequent blood counts and laboratory monitoring. Consequently, one of skill reading the Osborne references would understand that the kind of acne being treated is inflammatory acne caused by a microbial infection.

11. Traditional treatment of “black-heads” has involved washing with soap and water, skin abrasion and use of dissolving agents to loosen and remove the comedone plug within the pore. Sometimes removal is also accomplished by simple pressure. Under these circumstances, no inflammation is present and no inflammation results. The pore is cleared of the plug. One would not use an anti-microbial agent to remove the plug because one would not expect an anti-microbial agent to be able to dissolve the plug, or otherwise loosen the plug. Anti-microbial agents do not have solvating or emulsifying ability and are not present in skin treatment lotions, cremes or ointments in amounts that would enable solvation or emulsification. They typically are present at concentrations of one-hundredths percent by weight, i.e., very small concentrations. Note that none of the three attached articles about acne and its treatment indicates that antibiotics such as tetracycline or erythromycin should be used to treat “blackheads.”

12. I have reviewed the clinical data presented in Examples 2 and 3 of the present application. I find that these data completely support the result that such a Dapsone formulation will significantly reduce the incidence of “black-heads” wholly apart from the incidence or absence of inflammatory acne.

13. In view of the traditional understanding of treatment for acne as I have discussed above, I am consequently surprised that use of a 1% Dapsone formulation, i.e., an anti-microbial formulation of a prescription drug, will successfully reduce “black-head” numbers of patients suffering from this skin problem. I find this result is surprising because anti-microbial agents are not used for such treatment. Moreover, the typical kind of treatment for “black-heads” utilizes large quantities of solubilizing and emulsifying agents such as soap and water and scrubbing. It would not be expected that an extremely small concentration of Dapsone, such as 1%, would also be effective, even if it were possible that Dapsone would have solubilizing and emulsifying properties. In fact, however, Dapsone does not have such solubilizing and emulsifying properties. Consequently, it is surprising to me that Dapsone works at all to clear non-inflammatory acne or “black-heads”.

14. I further declare and acknowledge that I am subject to 18 U.S.C § 1001 which provides that whoever in any matter within the jurisdiction of any department or agency of the United States knowingly and willfully falsifies, conceals or cover up by any trick, scheme, or device a material fact, or makes any false, fictitious or fraudulent statements or representations, or makes or uses any false writing or document knowing the same to contain any false, fictitious or fraudulent statement or entry, shall be fined not more than \$10,000 or imprisoned not more than five years, or both.

Robert W. Lathrop

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18 November 2004

Date

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Use of Systemic Agents in the Treatment of Acne Vulgaris

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 A patient information handout on using isotretinoin for acne, written by the authors of this article, is provided on page 1835.

Effective treatment of acne vulgaris can prevent emotional and physical scarring. Therapy varies according to the severity of the disease. Topical medication is generally adequate in clearing comedonal acne, while inflammatory acne usually requires the addition of oral medication. Systemic antibiotics are used most frequently and can be highly effective. Newer formulations of combined oral contraceptives are also helpful in modulating sebum production in the female patient. Severe nodulocystic acne that does not respond to topical retinoids and systemic antibiotics may be treated with isotretinoin. However, the side effect profile of this medication is extensive, and physicians should be well-versed in its potential adverse effects. (Am Fam Physician 2000;62:1823-30,1835-6.)

See editorial on page 1772.

Acne vulgaris, or common acne, is a skin disorder of the pilosebaceous unit that generally develops in adolescence and improves in adulthood. Adolescent males, in particular, can be severely affected by this disease, which, if left untreated, can cause scarring.

Pathophysiology of Acne

At least four factors are important in the development of acne: plugging of the hair follicle with abnormally cohesive-desquamated cells, sebaceous gland

hyperactivity, proliferation of bacteria (especially *Propionibacterium acnes*) within sebum and inflammation (Figure 1).

Earliest changes in the hair follicle occur when the follicular canal becomes blocked with abnormally keratinized desquamating cells. This plug starts above the opening of the sebaceous gland into the follicular canal and causes gradual expansion of cells and sebum within the canal. The plug becomes visible at the skin surface as a white papule ("whitehead," or closed comedo). If the opening of the follicular canal dilates, this plug protrudes from the canal and turns a dark color ("blackhead," or open comedo).

Although sebum production increases during adolescence (particularly in boys, because of androgen stimulation), increased sebum alone does not cause acne.

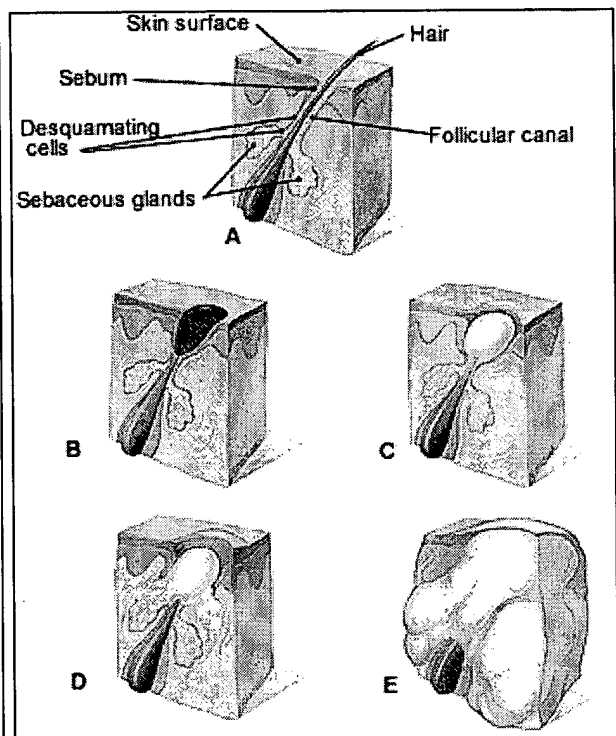
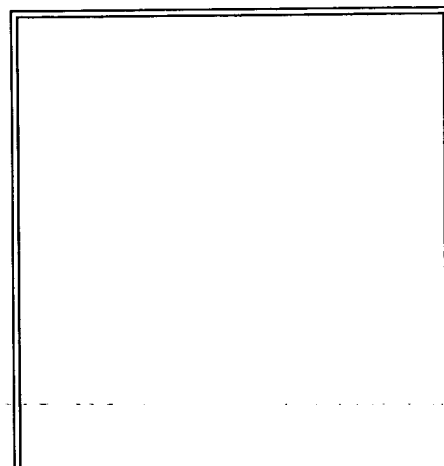


FIGURE 1. Stages of acne. (A) Normal follicle; (B) open comedo (blackhead); (C) closed comedo (whitehead); (D) papule; (E) pustule.

Bacteria, most importantly *P. acnes*, are present in increased numbers in persons who have acne. Much of the inflammation that eventually occurs arises from the action of enzymes produced by the bacteria. These enzymes hydrolyze sebum into free fatty acids, which stimulate the inflammatory process. Chemotactic factors are released by this reaction, attracting neutrophils. As the follicular wall becomes inflamed, an erythematous papule appears at the skin surface. With increased sebum production, obstruction and bacterial colonization, the follicular unit ruptures, spilling its contents into the dermis. The inflow of neutrophils causes the formation of pustules. Continuation of severe inflammation leads to formation of nodules and subsequent cysts.

Classification of Acne

Acne can be classified into three categories for the purposes of treatment: comedonal, inflammatory and nodulocystic (Table 1). Comedonal acne consists predominantly of open or closed comedones with little or no accompanying inflammation (Figure 2). This type of acne typically responds to topical keratolytic agents that decrease the cohesiveness of the follicular cells. Erythematous papules and pustules characterize inflammatory acne, but comedones may also be present (Figure 3). Topical agents alone may be insufficient to treat inflammatory acne, which may benefit from systemic antibiotics. Nodulocystic acne may consist of



comedones and inflammatory lesions, as well as deeper nodules and cysts (*Figure 4*). Although a six-month course of systemic antibiotics may be effective, nodulocystic acne frequently requires treatment with isotretinoin (Accutane). Before the initiation of isotretinoin therapy, however, patients should be evaluated for other causes of antibiotic treatment failure. Unusual causes of recalcitrant acne include drug-induced acne, tropical acne, acne conglobata and acne fulminans.

Systemic Therapy for Acne

Oral Antibiotics

Although topical therapy is generally adequate for comedonal acne, control of inflammatory acne usually requires systemic antibiotics. The antibiotics that have proved to be most effective include tetracycline, doxycycline (Vibramycin), minocycline (Minocin) and erythromycin. These drugs penetrate the follicle and sebaceous gland well and decrease colonization by *P. acnes*. They also have an anti-inflammatory effect independent of their antimicrobial properties. Although rare hypersensitivity reactions have been reported, the safety profile of these antibiotics is, in general, excellent, making routine laboratory monitoring in the asymptomatic, healthy patient unnecessary.^{1,2} Prescription guidelines for these antibiotics, as well as a detailed list of adverse reactions, are found in *Tables 2 and 3*.

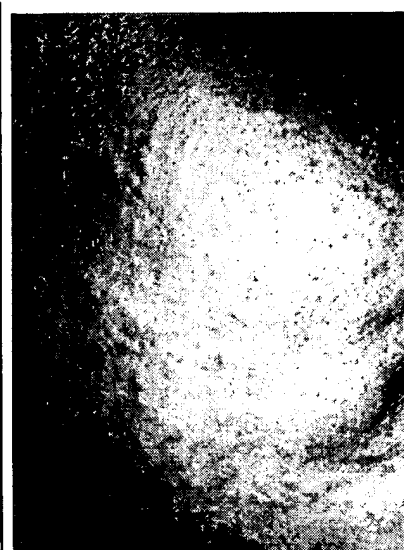


FIGURE 2. Comedonal acne. In closed comedones (whiteheads), a mass of desquamated cells plugs the follicular canal above the opening of the sebaceous gland. Sebum accumulates within the follicular canal and results in a white papule visible at the skin surface. In open comedones (blackheads), when the opening of the follicular canal dilates, the plug protrudes from the canal and turns a dark color.

Tetracycline is extremely inexpensive but may cause adverse effects, including vaginal yeast infections and dyspepsia (rarely, esophagitis with esophageal ulcerations). Other rare adverse effects include photosensitivity and pseudotumor cerebri. It is unclear whether tetracycline interferes with oral contraceptive efficacy and, therefore, young women are often counseled to use a back-up method of contraception while taking tetracycline.³ Tetracycline may cause discoloration of forming teeth and should not be given to pregnant women or to children younger than 13 years unless all permanent teeth have erupted. Although the tetracyclines have a long track record of safety, instances of single-organ dysfunction (most commonly, severe cutaneous reaction) have been reported, as well as a few cases of hypersensitivity reaction and serum sicknesslike reaction² (*Table 3*). Tetracycline therapy should be avoided in patients with renal or hepatic disease.

Doxycycline is a tetracycline derivative that exhibits excellent penetration into follicles and sebaceous glands. It is better tolerated than tetracycline and may be taken with food. Of the tetracycline derivatives, it is the one most likely to cause photosensitivity. Other adverse effects are similar to those of tetracycline.

TABLE 1

Treatment Options for Acne

Treatment	Comedonal acne	Inflammatory acne	Nodulocystic acne
<i>Topical therapy</i>			
Salicylic acid (Keralyt)	X		
Tretinoin (Retin-A)	X	X	
Azelaic acid (Azelex)	X	X	
Benzoyl peroxide	X	X	
Adapalene (Differin)	X	X	
Tazarotene (Tazorac)	X	X	
Antibiotics	X*	X	
<i>Systemic therapy</i>			
Oral contraceptives	X	X	X
Erythromycin		X	X
Tetracycline		X	X
Doxycycline (Vibramycin)		X	X
Minocycline (Minocin)			X
Isotretinoin (Accutane)			X

*--May be helpful if inflammatory lesions are present as well.

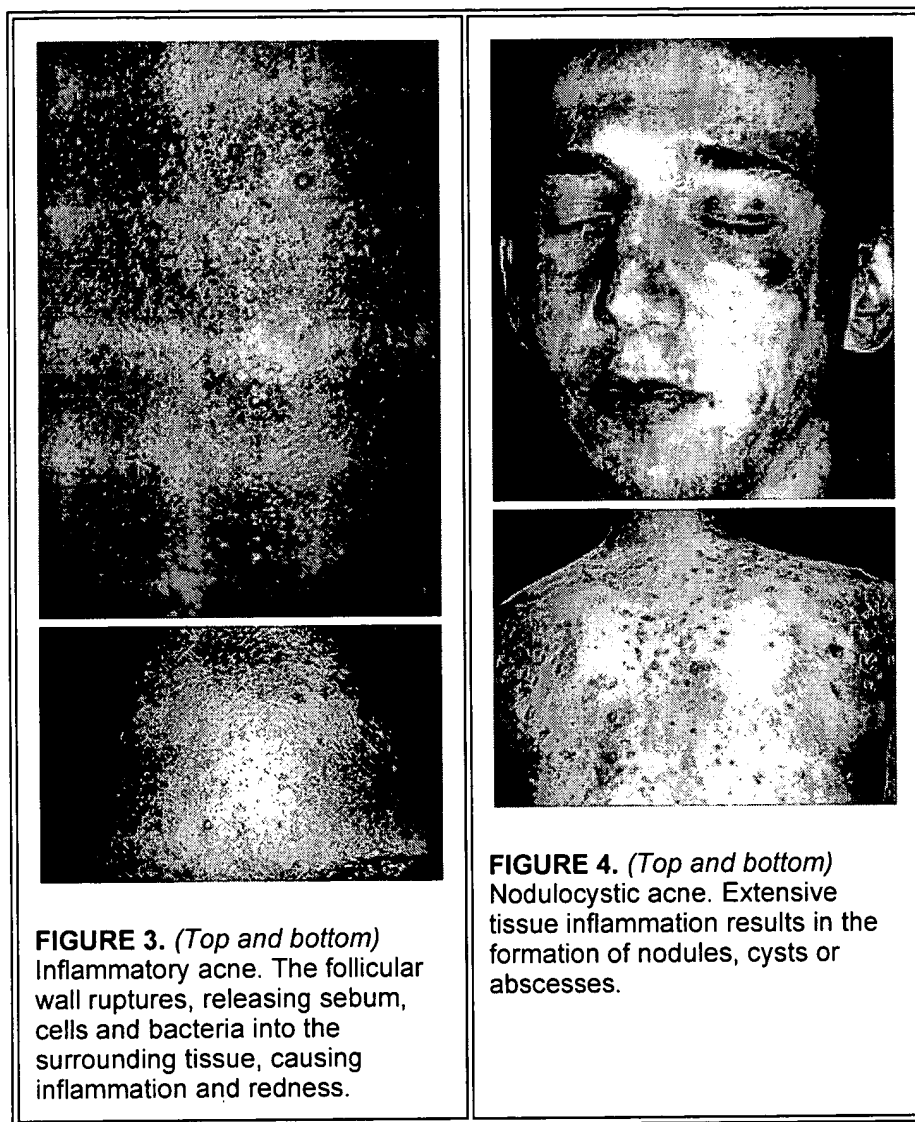
Minocycline is considered the most effective of the tetracycline derivatives, possibly because preexisting minocycline resistance is rare.⁴ It can be taken with food and, unlike the other tetracyclines, only infrequently causes photosensitivity. Most adverse effects of minocycline are similar to those of the other tetracyclines (*Table 3*). However, minocycline may cause cutaneous hyperpigmentation in scars, vertigo and, in rare instances, the development of a lupus-like syndrome. Minocycline is also associated with a higher frequency of hypersensitivity reactions than the other tetracyclines. Although hyperpigmentation is slow to fade, the other reactions usually resolve promptly with discontinuation of therapy.

Erythromycin is inexpensive but often causes dyspepsia or abdominal discomfort even when taken with meals. It is considered safe for use during pregnancy. However, *P. acnes* resistance to erythromycin develops more frequently (in as many as 60 percent of isolates) than with the other systemic antibiotics.

Much of the inflammation of acne results from the action of enzymes produced by *Propionibacterium acnes*.

If treatment fails despite compliance with systemic antibiotic therapy, two clinical entities

must be considered: antibiotic resistance and folliculitis related to overgrowth of gram-negative Enterobacteriaceae, Staphylococci or Malassezia yeasts.⁴ Aerobic and anaerobic cultures and sensitivity determinations should be used to decide on appropriate antibiotics. Gram-negative folliculitis is frequently treated with ampicillin, less commonly with trimethoprim-sulfamethoxazole (Bactrim, Septra) and, occasionally, with isotretinoin.^{5,6} The addition of topical benzoyl peroxide, a broad-spectrum antimicrobial agent, may also be beneficial in many patients who have folliculitis related to either bacteria or yeast.⁴



Hormone Therapy

Oral contraceptives may be a useful adjunctive therapy for all types of acne in women and adolescent girls. Sebum production is controlled by androgens, and oral contraceptives are known to reduce androgen levels by increasing sex hormonebinding globulin levels, thus reducing the availability of biologically active free testosterone.

The third-generation progestin norgestimate has lower intrinsic androgenicity than other currently available progestins⁷ and is effective in treating moderate inflammatory acne.^{8,9} Ortho Tri-Cyclen is a triphasic combination of norgestimate and ethinyl estradiol that has been labeled by the U.S. Food and Drug Administration (FDA) for the treatment of acne

vulgaris in women and adolescent girls. Other contraceptive agents that contain norgestimate (Ortho-Cyclen) or desogestrel (Desogen) are also reasonable choices. Two to four months of therapy may be required before improvement is seen, and relapses are common if medication is discontinued.

Adult women who present with acne in conjunction with hirsutism, alopecia or menstrual disturbances should be examined for the possibility of ovarian or adrenal hyperandrogenism.^{10,11} Basic screening tests

Inflammatory acne often requires treatment with oral antibiotics.

include measurement of free testosterone and dehydroepiandrosterone sulfate (DHEA-S) levels and the luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio. An elevated serum free testosterone level indicates a hyperandrogenous state of adrenal or ovarian origin; an increased DHEA-S level suggests adrenal hyperandrogenism and an LH/FSH ratio of greater than 3 suggests polycystic ovary syndrome. Consultation with an endocrinologist may be helpful in treating these conditions. Recalcitrant acne may respond to treatment with isotretinoin, low androgenic progestin oral contraceptives or other antiandrogens, such as spironolactone (Aldactone).¹¹⁻¹³

Although not labeled by the FDA for treatment of acne, spironolactone, at dosages of 100 to 200 mg daily, may be effective in treating acne vulgaris in most women and adolescent girls; frequent adverse effects include menstrual irregularities, breast tenderness and fatigue.¹⁴ Hyperkalemia is rarely a problem in adolescents taking spironolactone for acne.¹⁴

TABLE 2
Prescription Guidelines for Systemic Antibiotics

Antibiotic	Initial dosage*	Maintenance dosage	Comments
Tetracycline	500 mg twice daily	250 to 500 mg daily	Take on an empty stomach to avoid chelation with calcium, iron and other polyvalent cations. Take with a large glass of water to decrease dyspepsia.
Doxycycline (Vibramycin)	100 mg twice daily	50 to 100 mg daily	Take with meals.
Minocycline (Minocin)	50 to 100 mg twice daily	50 to 100 mg daily	Take with meals.
Erythromycin	500 mg twice daily	250 to 500 mg daily	Take with meals.

*--Initial dosages should be continued until clear improvement in acne is seen, usually three to six weeks.

Isotretinoin

Nodulocystic acne, if left untreated, may cause physical and emotional scarring. This form of acne is unlikely to respond to topical therapy. Initially, patients should be prescribed an oral antibiotic. If the acne fails to respond after six months of conventional therapy, treatment with isotretinoin should be considered.⁶

Isotretinoin is an oral retinoid preparation that decreases the size and secretion of the sebaceous glands, normalizes follicular keratinization, inhibits *P. acnes* growth and exerts an anti-inflammatory effect.¹⁵ Isotretinoin is labeled for use in patients with nodulocystic acne and can markedly improve this condition in most persons. There is a growing international consensus that, although the primary indication for isotretinoin is nodulocystic acne, patients who have an inadequate response to appropriate conventional therapy for less severe acne may also benefit from this drug.¹⁶ Patients who have scarring inflammatory acne and those with acne that causes severe psychologic distress may also be candidates.^{6,16} However, isotretinoin is FDA labeled only for treatment of severe recalcitrant nodular acne.¹⁷

The typical dosage of isotretinoin is 0.5 to 1 mg per kg daily in two divided doses, with a standard cumulative maximum of 120 to 150 mg per kg per treatment course.^{6,15,16,18,19} Because the intensity of the side effects of isotretinoin is dose-related, the lower dosage may be chosen. However, dosages of 0.5 mg per kg daily or less are more frequently associated with treatment failure.^{16,20} Initiation of isotretinoin therapy may cause a marked flare-up of the patient's acne. It is, therefore, common practice to introduce the medication slowly, beginning at 0.1 to 0.5 mg per kg daily, and increasing to the desired dosage of 1 mg per kg daily by the end of the first month of treatment.^{6,15} The average duration of therapy is five months, at which time most patients will have reached the desired goal of 120 to 150 mg per kg. However, a longer course of therapy is necessary in patients taking lower initial or daily dosages.

TABLE 3
Adverse Reactions Associated with Oral Antibiotic Use

Adverse reaction	Tetracycline	Doxycycline (Vibramycin)	Minocycline (Minocin)	Erythromycin
Dyspepsia	X	X	X	X
Vaginal yeast infection	X	X	X	X
Photosensitivity	X	X	X*	X
Possible interference with oral contraceptives	X	X	X	
Tooth discoloration in children younger than 13 years or in developing fetuses	X	X	X	
<i>Propionibacterium acnes</i> antibiotic resistance	X	X		X

Hyperpigmentation in scars			X
Pseudotumor cerebri	X	X	X
Vestibular toxicity			X
Lupus-like reaction† ²			X
Single-organ dysfunction‡ ²	X	X	X
Hypersensitivity reaction§ ²	X	X	X
Serum sicknesslike reaction ²	X	X	X

*--Photosensitivity occurs less commonly with minocycline than with other tetracyclines.

†--Absence of idiopathic systemic lupus erythematosus (SLE) and the presence of antinuclear antibody and at least one clinical feature of SLE that resolves with discontinuation of drug. May occur late after initiation of therapy.

‡--Severe disease in a single organ (e.g., severe cutaneous reaction, pneumonitis, pancreatitis, hepatitis)

§--Fever, skin eruption and internal organ involvement, developing within eight weeks of initiation of therapy.

||--Fever, skin eruption, arthralgia, ± lymphadenopathy, occurring within six weeks of initiation of treatment.

Adjuvant therapy with other agents may be considered during isotretinoin treatment. Topical antibiotics may be beneficial, but use of topical keratolytics and drying agents should be discontinued because concomitant use may lead to extensive dryness. Occasionally, oral erythromycin or prednisone is used at the beginning of isotretinoin therapy to control the initial acne flare-up. None of the tetracyclines should be used for this purpose because the combination of a tetracycline and isotretinoin increases the likelihood of pseudotumor cerebri development.²⁰

Pustules generally clear more rapidly than papules or nodules. Lesions on the face, upper arms and legs tend to respond more quickly than those on the trunk. After reaching the goal dosage of 120 to 150 mg per kg, isotretinoin therapy should be discontinued even if the acne is not completely clear because improvement continues for one to two months following cessation of treatment.

In a study of patients who were observed for 10 years, a single course of isotretinoin therapy completely cleared acne in more than 60 percent.¹⁶ If relapse occurred, it usually developed within the first three years after isotretinoin therapy; 78 percent of relapses were reported to occur within the first 18 months.¹⁶ Of the 39 percent of patients who experienced a relapse, 16 percent required re-initiation of oral antibiotics, and 23 percent required additional isotretinoin therapy.¹⁶ In those who relapse, repeated full courses of isotretinoin may be required. Of the 23 percent of patients who required repeated courses in one study, 17 percent had two courses, 5 percent had three courses and 1 percent had four to five courses, with predictably successful results and without additional adverse reactions.²¹

The side effect profile of isotretinoin is extensive, and physicians prescribing this medication should be well-versed in its potentially dangerous consequences. Patients should

be evaluated every four weeks for adverse effects and to ensure compliance with therapy.¹⁸ A reduction in dosage or cessation of therapy usually causes fairly rapid resolution of clinical and laboratory side effects.

Mucocutaneous reactions are the most common adverse effects.¹⁹ Drying of the mucosal surfaces occurs in nearly all users, with cheilitis being the most common finding. Frequent application of moisturizing agents is necessary. Many patients who wear contact lenses are forced to switch to eyeglasses during the course of therapy because of conjunctival dryness. Reddening of the skin and increased photosensitivity vary among different populations.¹⁹

More serious adverse effects are rare, and most involve the musculoskeletal system.¹⁹ Arthralgias and muscle stiffness occur more frequently in those who participate in vigorous exercise. Long-term retinoid therapy may be complicated by skeletal changes, including osteoporosis and osteophyte formation. However, no studies have reported notable bony changes associated with short-term isotretinoin therapy for the treatment of acne. Mild to moderate headaches are fairly common; if the headache is severe or associated with visual changes, the patient should be evaluated for the presence of pseudotumor cerebri, a rare consequence of therapy. Patients may complain of fatigue or mild mood alterations and, rarely, isotretinoin may precipitate a depression. There have been reports of patients committing suicide while taking isotretinoin, and patients at risk should be monitored carefully.²²

Laboratory monitoring is required to assess adverse metabolic events (*Table 4*). Disturbances in lipid metabolism resulting in hypertriglyceridemia and hypercholesterolemia occur in as many as 25 percent of patients. Liver enzyme levels should also be monitored periodically, although elevations beyond the reference range are rare.¹⁹ Although opinions vary, most physicians routinely measure liver enzyme and lipid levels at the start of therapy and again two to four weeks later.^{18,19} If no abnormal results are found at this point, some recommend discontinuing periodic testing,¹⁹ while others continue to test every four to eight weeks.¹⁸ If elevations occur, reducing the dosage or, in rare instances, discontinuing isotretinoin therapy should be considered.⁶

TABLE 4
Recommended Laboratory Monitoring for Patients Using Isotretinoin

Test	Frequency	Comments
Qualitative hCG (urine pregnancy tests are adequate if they meet the required sensitivity of 50 IU per L)*	One week before starting treatment, then monthly* Monthly pregnancy tests may be replaced by detailed questioning about contraceptive use, menses, etc., at monthly visits	Two forms of birth control (e.g., oral contraceptive plus barrier method) required; isotretinoin treatment should begin on the second or third day after the onset of a normal menstrual period; pregnancy should not be attempted until one month after discontinuation of therapy.*
Lipid levels*	Before starting treatment,	Measure fasting triglyceride levels; if level

	then at weekly or biweekly intervals until the lipid response to isotretinoin is established, usually by four weeks*	rises to 350 mg per dL (3.95 mmol per L), repeat in two weeks. Isotretinoin therapy should be discontinued if levels exceed 700 mg per dL (7.9 mmol per L).
Liver function tests*	Before starting treatment, then at weekly or biweekly intervals until weekly or biweekly isotretinoin is established*	If elevations appear, reduce the dosage by 50 percent or interrupt treatment.

hCG = human chorionic gonadotropin.

*--Official U.S. Food and Drug Administration labeling requirements.

The most devastating adverse effect of isotretinoin is teratogenicity. Major malformations may occur in 25 to 30 percent of fetuses exposed to isotretinoin.²³ The most common developmental defects involve craniofacial, cardiac, thymic and central nervous system structures.²³ Despite a pregnancy prevention program implemented by the manufacturer, pregnancy occurs in 3.4 per 1,000 courses of treatment with isotretinoin.²⁴ Physicians are encouraged to use the "Patient Information and Consent to Treatment" form, which is available from the manufacturer, when counseling patients. Before therapy begins, the patient must be proved not to be pregnant, and two concurrent, effective forms of birth control should be used for one month before beginning isotretinoin therapy, throughout the entire course of treatment and for one month after cessation of therapy.²⁵

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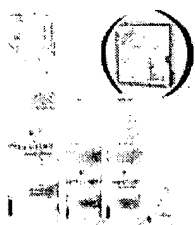
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What Is Acne?

Acne is a disorder resulting from the action of hormones on the skin's oil glands (sebaceous glands), which leads to plugged pores and outbreaks of lesions commonly called pimples or zits. Acne lesions usually occur on the face, neck, back, chest, and shoulders. Nearly 17 million people in the United States have acne, making it the most common skin disease. Although acne is not a serious health threat, severe acne can lead to disfiguring, permanent scarring, which can be upsetting to people who are affected by the disorder.

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How Does Acne Develop?

Doctors describe acne as a disease of the pilosebaceous units

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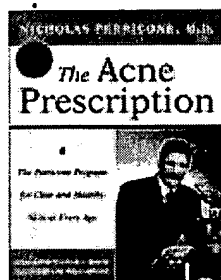
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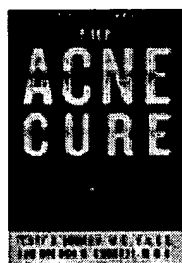
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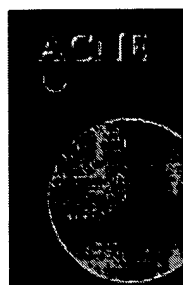
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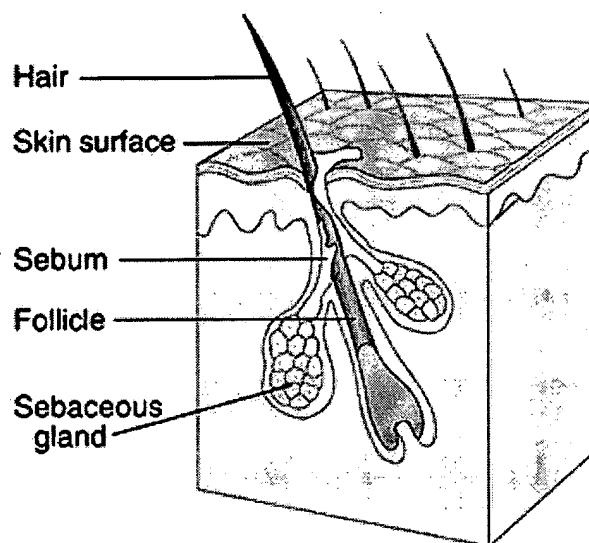
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(PSUs). Found over most of the body, PSUs consist of a sebaceous gland connected to a canal, called a follicle, that contains a fine hair (see "Normal Pilosebaceous Unit" diagram, below). These units are most numerous on the face, upper back, and chest. The sebaceous glands make an oily substance called sebum that normally empties onto the skin surface through the opening of the follicle, commonly called a pore. Cells called keratinocytes line the follicle.

Normal Pilosebaceous Unit

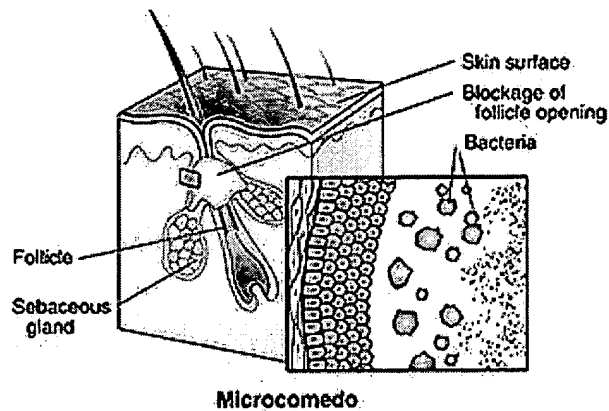


The hair, sebum, and keratinocytes that fill the narrow follicle may produce a plug, which is an early sign of acne. The plug prevents sebum from reaching the surface of the skin through a pore. The mixture of oil and cells allows bacteria *Propionibacterium acnes* (*P. acnes*) that normally live on the skin to grow in the plugged follicles. These bacteria produce chemicals and enzymes and attract white blood cells that cause inflammation. (Inflammation is a characteristic reaction of tissues to disease or injury and is marked by four signs: swelling, redness, heat, and pain.) When the wall of the plugged follicle breaks down, it spills everything into the nearby skin--sebum, shed skin cells, and bacteria--leading to lesions or pimples.

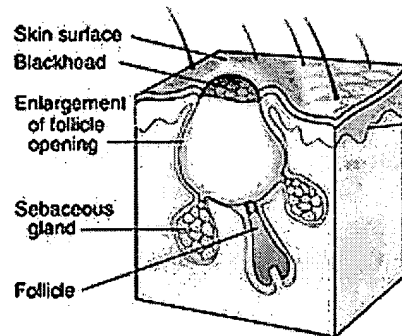
People with acne frequently have a variety of lesions, some of which are shown in the diagrams below. The basic acne lesion, called the comedo (KOM-e-do), is simply an enlarged and plugged hair follicle. If the plugged follicle, or comedo, stays beneath the skin, it is called a closed comedo and produces a white bump called a whitehead. A comedo that reaches the surface of the skin and opens up is called a blackhead because it looks black on the skin's surface. This black discoloration is not due to dirt. Both whiteheads and

blackheads may stay in the skin for a long time.

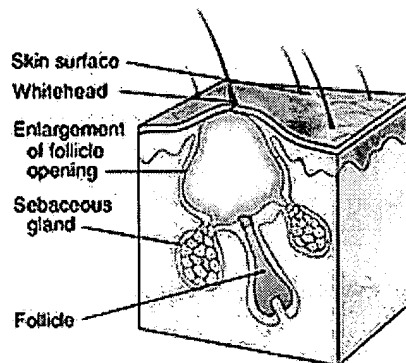
Types of Lesions



Microcomedo



Open Comedo (Blackhead)



Closed Comedo (Whitehead)

Other troublesome acne lesions can develop, including the following:

- **Papules**--inflamed lesions that usually appear as small, pink bumps on the skin and can be tender to the touch
- **Pustules (pimples)**--papules topped by pus-filled lesions that may be red at the base
- **Nodules**--large, painful, solid lesions that are lodged

- deep within the skin
- **Cysts**--deep, painful, pus-filled lesions that can cause scarring.

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What Causes Acne?

The exact cause of acne is unknown, but doctors believe it results from several related factors. One important factor is an increase in hormones called androgens (male sex hormones). These increase in both boys and girls during puberty and cause the sebaceous glands to enlarge and make more sebum. Hormonal changes related to pregnancy or starting or stopping birth control pills can also cause acne.

Another factor is heredity or genetics. Researchers believe that the tendency to develop acne can be inherited from parents. For example, studies have shown that many school-age boys with acne have a family history of the disorder. Certain drugs, including androgens and lithium, are known to cause acne. Greasy cosmetics may alter the cells of the follicles and make them stick together, producing a plug.

Factors That Can Make Acne Worse

Factors that can cause an acne flare include:

- Changing hormone levels in adolescent girls and adult women 2 to 7 days before their menstrual period starts
- Friction caused by leaning on or rubbing the skin
- Pressure from bike helmets, backpacks, or tight collars
- Environmental irritants, such as pollution and high humidity
- Squeezing or picking at blemishes
- Hard scrubbing of the skin.

Myths About the Causes of Acne

There are many myths about what causes acne. Chocolate and greasy foods are often blamed, but foods seem to have little effect on the development and course of acne in most people. Another common myth is that dirty skin causes acne; however, blackheads and other acne lesions are not caused by dirt. Finally, stress does not cause acne.

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Who Gets Acne?

People of all races and ages get acne. It is most common in adolescents and young adults. Nearly 85 percent of people between the ages of 12 and 24 develop the disorder. For most people, acne tends to go away by the time they reach their thirties; however, some people in their forties and fifties continue to have this skin problem.

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Methods of Acne Treatment?

Acne is often treated by dermatologists (doctors who specialize in skin problems). These doctors treat all kinds of acne, particularly severe cases. Doctors who are general or family practitioners, pediatricians, or internists may treat patients with milder cases of acne.

The goals of treatment are to heal existing lesions, stop new lesions from forming, prevent scarring, and minimize the psychological stress and embarrassment caused by this disease. Drug treatment is aimed at reducing several problems that play a part in causing acne: abnormal clumping of cells in the follicles, increased oil production, bacteria, and inflammation. Depending on the extent of the person's acne, the doctor will recommend one of several over-the-counter (OTC) medicines or prescription medicines that are topical (applied to the skin) or systemic (taken by mouth). The doctor may suggest using more than one topical medicine or combining oral and topical medicines.

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Blackheads, Whiteheads, and Mild Inflammatory Acne Treatment

Doctors usually recommend an OTC or prescription topical medication for people with mild signs of acne. Topical medicine is applied directly to the acne lesions or to the entire area of affected skin.

Benzoyl peroxide, resorcinol, salicylic acid, and sulfur are the most common topical OTC medicines used to treat acne. Each works a little differently. Benzoyl peroxide is best at killing *P. acnes* and may reduce oil production. Resorcinol, salicylic acid, and sulfur help break down blackheads and whiteheads.

Salicylic acid also helps cut down the shedding of cells lining the follicles of the oil glands. Topical OTC medications are available in many forms, such as gel, lotion, cream, soap, or pad.

In some patients, OTC acne medicines may cause side effects such as skin irritation, burning, or redness. Some people find that the side effects lessen or go away with continued use of the medicine. Severe or prolonged side effects should be reported to the doctor.

OTC topical medicines are somewhat effective in treating acne when used regularly. Patients must keep in mind that it can take 8 weeks or more before they notice their skin looks and feels better.

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Moderate to Severe Inflammatory Acne Treatment

Patients with moderate to severe inflammatory acne may be treated with prescription topical or oral medicines, alone or in combination.

Prescription Topical Medicines

Several types of prescription topical medicines are used to treat acne, including antibiotics, benzoyl peroxide, tretinoin, adapalene, and azelaic acid. Antibiotics and azelaic acid help stop or slow the growth of bacteria and reduce inflammation. Tretinoin, a type of drug called a retinoid that contains an altered form of vitamin A, is an effective topical medicine for stopping the development of new comedones. It works by unplugging existing comedones, thereby allowing other topical medicines, such as antibiotics, to enter the follicles. The doctor may also prescribe newer retinoids or retinoid-like drugs, such as tazarotene or adapalene, that help decrease comedo formation.

Like OTC topical medicines, prescription topical medicines come as creams, lotions, solutions, or gels. The doctor will consider the patient's skin type when prescribing a product. Creams and lotions provide moisture and tend to be good for people with sensitive skin. Gels and solutions are generally alcohol based and tend to dry the skin. Therefore, patients with very oily skin or those who live in hot, humid climates may prefer them. The doctor will tell the patient how to apply the medicine and how often to use it.

Some people develop side effects from using prescription topical medicines. Initially, the skin may look worse before improving. Common side effects include stinging, burning, redness, peeling, scaling, or discoloration of the skin. With some medicines, like retinoids, these side effects usually decrease or go away after the medicine is used for a period of time. Patients should report prolonged or severe side effects to their doctor. Between 4 and 8 weeks will most likely pass before patients see their skin improve.

Prescription Oral Medicines

For patients with moderate to severe acne, the doctor often prescribes oral antibiotics (taken by mouth). Oral antibiotics are thought to help control acne by curbing the growth of bacteria and reducing inflammation. Prescription oral and topical medicines may be combined. For example, benzoyl peroxide may be combined with clindamycin, erythromycin, or sulfur. Other common antibiotics used to treat acne are tetracycline, minocycline, and doxycycline. Some people have side effects when taking these antibiotics, such as an increased tendency to sunburn, upset stomach, dizziness or lightheadedness, and changes in skin color. Tetracycline is not given to pregnant women, nor is it given to children under 8 years of age because it might discolor developing teeth. Tetracycline and minocycline may also decrease the effectiveness of birth control pills. Therefore, a backup or another form of birth control may be needed. Prolonged treatment with oral antibiotics may be necessary to achieve the desired results.

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Severe Nodular or Cystic Acne Treatment

Acne where infections are deep under the skin and do not raise to the surface of skin is called severe nodular acne or cystic acne. Cystic acne heals very slowly as infection waste material is not discharged. People with nodules or cysts should be treated by a dermatologist. For patients with severe inflammatory acne that does not improve with medicines such as severe nodular or cystic acne, a doctor may prescribe isotretinoin (Accutane*), a retinoid. Isotretinoin is an oral drug that is usually taken once or twice a day with food for 15 to 20 weeks. It markedly reduces the size of the oil glands so that much less oil is produced. As a result, the growth of bacteria is decreased.

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not mean that these products are endorsed by HealthNewsflash. Also, if a particular brand name is not mentioned, this does not mean or imply that the product is unsatisfactory.

Advantages of Isotretinoin (Accutane)

Isotretinoin is a very effective medicine that can help prevent scarring. After 15 to 20 weeks of treatment with isotretinoin, acne completely or almost completely goes away in up to 90 percent of patients. In those patients where acne recurs after a course of isotretinoin, the doctor may institute another course of the same treatment or prescribe other medicines.

Disadvantages of Isotretinoin (Accutane)

Isotretinoin can cause birth defects in the developing fetus of a pregnant woman. **It is important that women of childbearing age are not pregnant and do not get pregnant while taking this medicine.** Women must use two separate effective forms of birth control at the same time for 1 month before treatment begins, during the entire course of treatment, and for 1 full month after stopping the drug. They should ask their doctor when it is safe to get pregnant after they have stopped taking Accutane.

Some people with acne become depressed by the changes in the appearance of their skin. Changes in mental health may be intensified during treatment or soon after completing a course of medicines like Accutane. A doctor should be consulted if a person feels unusually sad or has other symptoms of depression, such as loss of appetite or trouble concentrating.

Other possible side effects include dry eyes, mouth, lips, nose, or skin; itching; nosebleeds; muscle aches; sensitivity to the sun; and, sometimes, poor night vision. More serious side effects include changes in the blood, such as an increase in triglycerides and cholesterol, or a change in liver function. To make sure Accutane is stopped if side effects occur, the doctor monitors blood studies that are done before treatment is started and periodically during treatment. Side effects usually go away after the medicine is stopped.

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Hormonally Influenced Acne Treatment in Women

Clues that help the doctor determine whether acne in an adult woman is due to an excess of androgen hormones are hirsutism (excessive growth of hair in unusual places), premenstrual acne flares, irregular menstrual cycles, and

elevated blood levels of certain androgens. The doctor may prescribe one of several drugs to treat women with this type of acne. Low-dose estrogen birth control pills help suppress the androgen produced by the ovaries. Low-dose corticosteroid drugs, such as prednisone or dexamethasone, may suppress the androgen produced by the adrenal glands. Finally, the doctor may prescribe an antiandrogen drug, such as spironolactone (Aldactone). This medicine reduces excessive oil production. Side effects of antiandrogen drugs may include irregular menstruation, tender breasts, headache, and fatigue.

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Other Acne Treatments

Doctors may use other types of procedures in addition to drug therapy to treat patients with acne. For example, the doctor may remove the patient's comedones during office visits. Sometimes the doctor will inject cortisone directly into lesions to help reduce the size and pain of inflamed cysts and nodules.

Early treatment is the best way to prevent acne scars. Once scarring has occurred, the doctor may suggest a medical or surgical procedure to help reduce the scars. A superficial laser may be used to treat irregular scars. Another kind of laser allows energy to go deeper into the skin and tighten the underlying tissue and plump out depressed scars. Dermabrasion (or microdermabrasion), which is a form of "sanding down" scars, is sometimes combined with the subsurface laser treatment. Another treatment option for deep scars caused by cystic acne is the transfer of fat from one part of the body to the face.

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Skin Care and Acne Treatment

Clean Skin Gently

Most doctors recommend that people with acne gently wash their skin with a mild cleanser, once in the morning and once in the evening and after heavy exercise. Some people with acne may try to stop outbreaks and oil production by scrubbing their skin and using strong detergent soaps and rough scrub pads. However, scrubbing will not improve acne;

in fact, it can make the problem worse. Patients should ask their doctor or another health professional for advice on the best type of cleanser to use. Patients should wash their face from under the jaw to the hairline. It is important that patients thoroughly rinse their skin after washing it. Astringents are not recommended unless the skin is very oily, and then they should be used only on oily spots. Doctors also recommend that patients regularly shampoo their hair. Those with oily hair may want to shampoo it every day.

Avoid Frequent Handling of the Skin

People who squeeze, pinch, or pick their blemishes risk developing scars or dark blotches. People should avoid rubbing and touching their skin lesions.

Shave Carefully

Men who shave and who have acne can test both electric and safety razors to see which is more comfortable. Men who use a safety razor should use a sharp blade and soften their beard thoroughly with soap and water before applying shaving cream. Nicking blemishes can be avoided by shaving lightly and only when necessary.

Avoid a Sunburn or Suntan

Many of the medicines used to treat acne can make a person more prone to sunburn. A sunburn that reddens the skin or suntan that darkens the skin may make blemishes less visible and make the skin feel drier. However, these benefits are only temporary, and there are known risks of excessive sun exposure, such as more rapid skin aging and a risk of developing skin cancer.

Choose Cosmetics Carefully

People being treated for acne often need to change some of the cosmetics they use. All cosmetics, such as foundation, blush, eye shadow, and moisturizers, should be oil free. Patients may find it difficult to apply foundation evenly during the first few weeks of treatment because the skin may be red or scaly, particularly with the use of topical tretinoin or benzoyl peroxide. Oily hair products may eventually spread over the forehead, causing closed comedones. Products that are labeled as noncomedogenic (do not promote the formation of closed pores) should be used; in some people, however, even these products may cause acne.

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What Research Is Being Done on Acne?

Medical researchers are working on new drugs to treat acne, particularly topical antibiotics to replace some of those in current use. As with many other types of bacterial infections, doctors are finding that, over time, the bacteria that are associated with acne are becoming resistant to treatment with certain antibiotics. Research is also being conducted by industry on the potential side effects of isotretinoin and the long-term use of medicines used for treating acne.

Scientists are working on other means of treating acne. For example, researchers are studying the biology of sebaceous cells and testing a laser in laboratory animals to treat acne by disrupting sebaceous glands. Scientists are also studying the treatment of androgenic disorders, including acne, in men by inhibiting an enzyme that changes testosterone to a more potent androgen.

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Acne in Adolescents

A 15 year old adolescent male seeks a preparticipation sports physical. He is healthy, and he has no questions, complaints, or concerns. The adolescent is well developed and well nourished, with normal vital signs, including blood pressure. The physical is entirely normal except for the skin. Erythematous pustules are present across the hairline, and cystic lesions are evident over both cheeks. Scattered blackheads are located over the nose and cheeks as well. The chest and back are clear with no lesions. What is the pathogenesis of acne vulgaris? What are some contributing factors in the development of acne? What are the different types of acne lesions? What management options are available for the treatment of mild, moderate, and severe acne in adolescents? What are the indications for the use of isotretinoin (Accutane®)? What is the prognosis for adolescent patients with acne?

Acne vulgaris is a common condition that most frequently occurs in adolescents. The disease can be devastating to adolescents both physically and psychologically. Primary care physicians should therefore acknowledge acne as a medical problem even when patients do not mention it (as in the vignette above) and treat the condition accordingly.

EPIDEMIOLOGY

Most cases of acne that require treatment occur in individuals 9 to 19 years of age, although the condition can also affect young infants. Boys and girls are equally affected but the condition is usually more severe in boys. No ethnic groups are predisposed to acne, but certain cultural practices, such as the use of oily grooming agents can lead to a specific pattern of lesions. Estimates indicate that more than 85% of adolescents in the USA are affected with acne and that more than \$124 million dollars is spent annually on acne treatments. Internal agents include endogenous hormones (androgens, progesterone) and specific drugs (oral contraceptives, isoniazid, phenytoin, corticosteroids, lithium-containing compounds). External agents include skin bacteria, especially *Propionibacterium acnes*; industrial chemicals (petroleum, animal and vegetable oils); oil- or wax-containing cosmetics; greasy sunscreen or suntan preparations; and local pressure from objects such as headbands, shoulder pads, or helmets. Excessive perspiration and emotional stress can also aggravate acne. Specific foods such as chocolate, soda, and french fries have not been shown to cause or worsen acne.

CLINICAL PRESENTATION

The lesions of acne vulgaris primarily affect the face, chest, back, and shoulders, and can be noninflamed or inflamed papules, and/or pustules. Open comedones (blackheads) contain central dark material; closed comedones (whiteheads) are small flesh-colored bumps. Inflamed lesions are typically erythematous papules or pustules and may be cystic in appearance.

PATHOPHYSIOLOGY

Although the etiology remains unclear, the pathogenesis involves certain processes. 1.) Abnormal follicular keratinization. The earliest change in the formation of acne occurs in the horny cells that line the sebaceous follicle. A disturbance in the differentiation of these cells leads to excessive shedding of the cells into the lumen. Impaction of the follicle occurs as these horny cells stick together. 2.) Overproduction of sebum. The sebaceous gland is highly responsive to hormonal stimulation, namely androgens. With the rise in androgens during puberty, hypertrophy of the sebaceous gland occurs and the production of sebum is increased. The flow of sebum is obstructed by the above follicular keratinization, resulting in retention of all material. 3.) Proliferation of *P. acnes*. The overproduction of sebum in acne provides a good environment for the proliferation of *P. acnes*, an anaerobic diptheroid that along with *Staph. epidermis* and *Pityrosporum ovale*, is part of the microflora of the sebaceous follicle. In addition

P. acnes possesses a lipase that hydrolyzes sebum triglycerides into free fatty acids. These acids irritate the follicular wall and cause inflammation. 4.) Inflammation. The expulsion of sebum into the dermal layer of the skin occurs as a result of the rupture of the pilosebaceous follicle. This initiates an inflammatory process and the formation of inflammatory lesions such as pustules and cysts. *P. acnes* produces biologically active extracellular materials, which increase the permeability of the follicular epithelium. The bacterium also produces chemotactic factors that are responsible for the migration of inflammatory cells to the area.

HISTORY

The primary historical issues are to establish how long the acne has been present and if the condition has ever been treated. Psychological aspects should include questions to assess the patient's overall self-esteem. Expectations regarding treatment and recovery should also be assessed at the initial visit before therapy is begun.

PHYSICAL EXAM

This should focus in the primary sites of acne: face, chest, back, and shoulders. The entire skin should be inspected closely at the first visit. Individual lesions should be checked for signs of inflammation and infection at each follow-up visit. Their distribution should also be recorded along with their response to treatment. The presence or absence of scarring should also be assessed as a measure of the severity of acne and a predictor of outcome.

LABORATORY TESTS

No laboratory studies are needed either at the time of the initial evaluation or during the treatment of mild to moderate acne. In the case of severe acne, when isotretinoin is indicated, several pretreatment studies are necessary: CBC, liver function tests, and a fasting lipid profile are recommended. In addition, a pregnancy test must be performed within two weeks of starting isotretinoin in sexually active female adolescents. These studies should be obtained in consultation with a dermatologist, who is generally responsible for prescribing isotretinoin.

MANAGEMENT

The general management of acne should include patient education regarding the pathophysiology of the condition to dispel any myths regarding its etiology and treatment. In addition, the patient's motivation should be assessed to better individualize therapy. Parental involvement is optimal in cases of severe acne. All adolescents with acne should follow these general recommendations:

- Wash skin with mild soap and water once or twice daily.
- Use cosmetics sparingly or switch to oil-free products.
- Avoid picking and excessive scrubbing.
- Note that dietary modifications are not indicated.
- Follow the prescribed regimen carefully

(See Table below).

The specific therapies prescribed depend on the severity of the acne and patients' ability to comply with the proposed treatment. Combination therapy is used and later modified according to patients' response. Physicians should remember that the acne often looks worse before it gets better. Noticeable improvement usually takes four to six weeks.

Treatment of Acne

Grade One	Benzoyl peroxide 5% of 10% every other day, or once a day
Grade Two	Benzoyl peroxide as above plus topical antibiotics BID. Retinoic acid in resistant cases
Grade Three	Benzoyl peroxide 10% BID, (may alternate with retinoic acid once a day) plus oral antibiotics
Grade Four	Above treatment for G3 plus referral to a dermatologist for possible treatment with isotretinoin

Topical Therapy

Several topical products are available for the treatment of acne. Benzoyl peroxide is bactericidal for *P. acnes* and acts as a comedolytic agents as well. Although over-the-counter lotions are available, the more effective gel preparations are preferable. The lowest concentration possible should be used initially. Higher concentrations should be used in cases in which the trunk or the back are involved. Tretinoin or retinoic acid (Retin-A) is the mainstay of therapy for noninflammatory acne. This vitamin A derivative reduces micromedo formation by normalizing follicular keratinization and decreasing the adhesiveness of horny cells shed into the follicular lumen. Like benzoyl peroxide, retinoic acid can be very irritating and may cause some peeling. Therefore therapy should be initiated cautiously with a cream or gel, which is less potent and drying than the liquid preparation. To reduce irritation, patients should be instructed to wash with a mild soap no more than two times a day and to wait at least 20 to 30 minutes for the skin to dry completely before applying the product. Physicians often recommend that patients apply retinoic acid before bedtime rather than in the mornings, which tend to be more hectic. Caution against excessive sun exposure must be stressed. Antibiotic Therapy. Both topical as well as systemic antibiotics can be used in the treatment of inflammatory acne. Topical antibiotics are often useful in patients with inflammatory lesions that are unresponsive to benzoyl peroxide or retinoic acid alone. Such antibiotics act by inhibiting the growth of *P. acnes* and reducing the number of comedones, papules, and pustules. Erythromycin, tetracycline, clindamycin, and meclocycline are available as topical preparations. The erythromycin gel is most popular; the recommended dosage is twice daily. Allergic reactions from topical formulations rarely occur. Compared to systemic antibiotics, topical preparations have fewer side effects because of decreased absorption. Systemic antibiotics are the mainstay of therapy in patients with nodular or cystic inflammatory acne and in patients who have not responded to topical antibiotics. However, systemic agents have not been shown to be effective with comedonal acne. Hormonal therapy is indicated in females over 16 years of age who are unresponsive to other forms of treatment and who are not candidates for isotretinoin. High-dose estrogen suppresses sebum production. It cannot be used in males because of its feminizing effects. They are usually prescribed as oral contraceptives for 21 days. Low-dose glucocorticoids are indicated in females with acne accompanied by virilization or any other evidence of excessive androgens. Isotretinoin (Accutane) is currently the most effective treatment for severe pustulocystic acne that is resistant to conventional therapy. This agent is also useful in patients with a propensity for scarring. The most significant side effect is teratogenicity, therefore isotretinoin should be used cautiously in women of childbearing age, and the drug should not be prescribed in pregnant or nursing women. (Taken from: Pediatrics: A Primary Care Approach; Acne by Monica Sifuentes, MD; Saunders)

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